

5TH
**World Congress of
Cutaneous Lymphomas**



Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Biologic Insights| #192

Tracing the evolutionary origins and transcriptomic variability in Sézary syndrome and mycosis fungoides

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CANCER CENTER**



Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

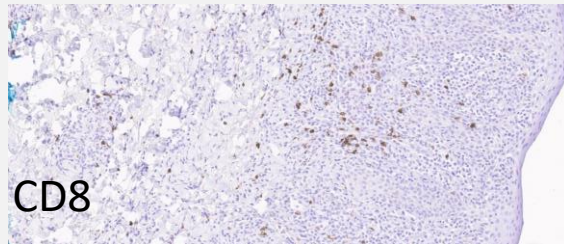
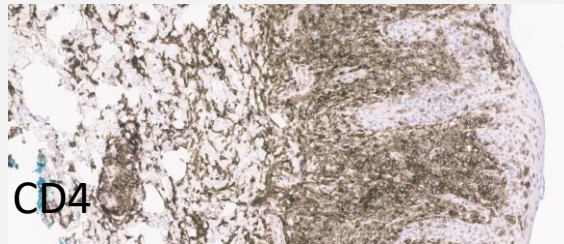
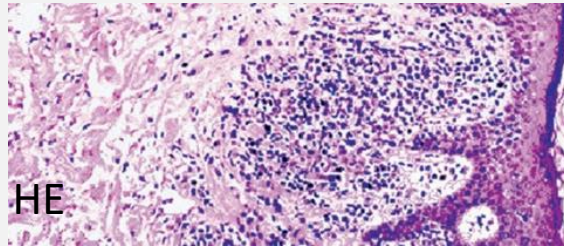
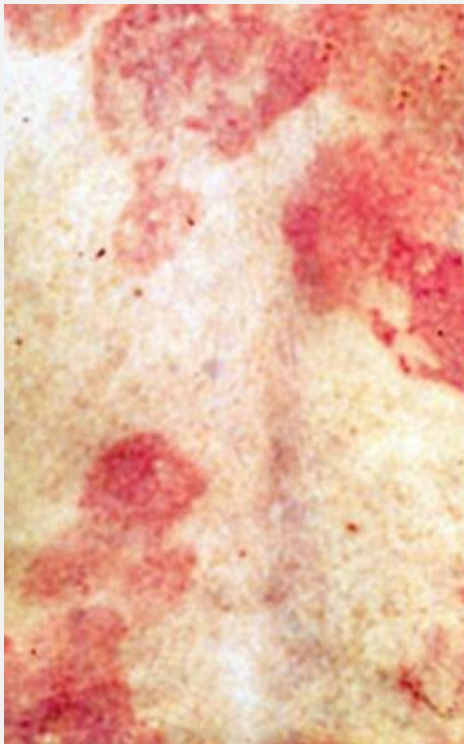
The off-label/investigational use of dupilumab will be addressed.

Is Sézary Syndrome related to MF?

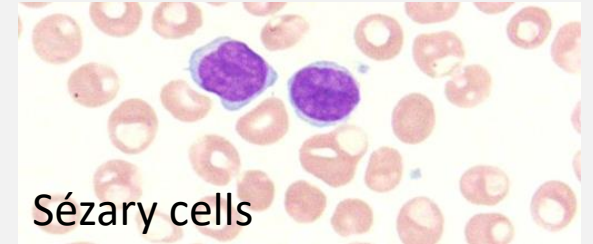
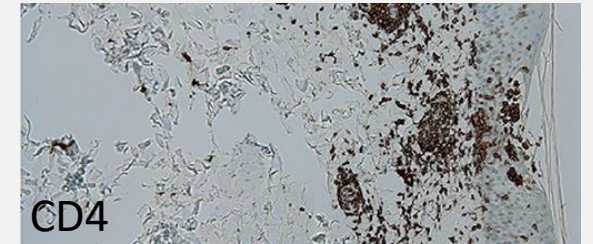
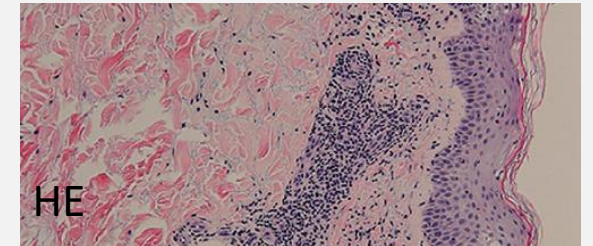
Mycosis Fungoides (MF)

Vs

Sézary Syndrome (SS)



[LeBlanc RE. Mycosis Fungoides. www.pathologyoutlines.com. 2022]



[Kamijo H, et al. *J Dermatol*. 2019; Lazarchick J *ASH Image Bank*. 2010]

Skin resident effector memory T cells

Central memory T cells

Mycosis Fungoides (MF)

Vs

Sézary Syndrome (SS)



ELSEVIER

Journal of the American Academy of Dermatology

Volume 77, Issue 4, October 2017, Pages 719-727



Original article

Early clinical manifestations of Sézary syndrome: A multicenter retrospective cohort study

Aaron R. Mangold MD^a, Agnieszka K. Thompson MD^{b,c}, Mark D. Davis MD^b, Ieva Saulite MD^d, Antonio Cozzio MD^{d,e}, Emmanuella Guenova MD, PhD^{d,e}, Emilia Hodak MD, PhD^f, Iris Amitay-Laish MD^f, Ramon M. Pujol MD, PhD^g, Mark R. Pittelkow MD^a, Robert Gniadecki MD, PhD^{h,i}

[LeBlanc RE. Mycosis Fungoides. *www.pathologyoutlines.com*. 2022]



Characteristic

Value, N=263

Earliest recorded signs

Nonspecific dermatitis, n (%)[†]

129 (49.0)

Erythroderma, n (%)

66 (25.1)

Patches and plaques suggestive of MF or parapsoriasis, n (%)

28 (10.6)

Leukemia without erythroderma, n (%)

23 (8.7)

AD-like lesions, n (%)

13 (4.9)

Isolated lymphadenopathy, n (%)

1 (0.4)

Urticaria followed by dermatitis, n (%)

1 (0.4)

Unknown, n (%)

2 (0.8)

[Kamijo H, et al. *J Dermatol*. 2019; Lazarcnick J *ASH Image Bank*. 2010]

Skin resident effector memory T cells

Central memory T cells

Mycosis Fungoides (MF)

Vs

Sézary Syndrome (SS)

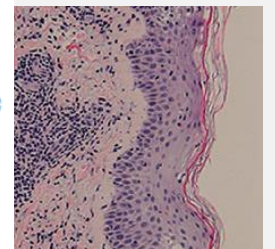


Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors

BRIEF REPORT | AUGUST 5, 2010

Brief Report

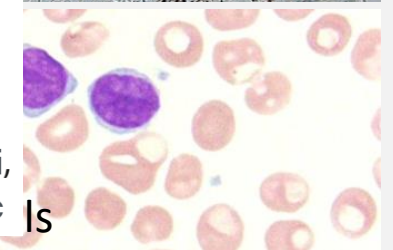
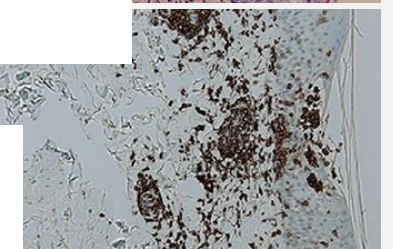
James J. Campbell, Rachael A. Clark, Rei Watanabe, Thomas S. Kupper



LETTER TO BLOOD | SEPTEMBER 21, 2017

Circulating and skin-derived Sézary cells: clonal but with phenotypic plasticity

Marie Roelens, Marc Delord, Caroline Ram-Wolff, Anne Marie-Cardine, Antonio Alberdi, Guitta Maki, Laurence Homyrda, Armand Bensussan, Martine Bagot, Antoine Toubert, H el ene Moins-Teisserenc

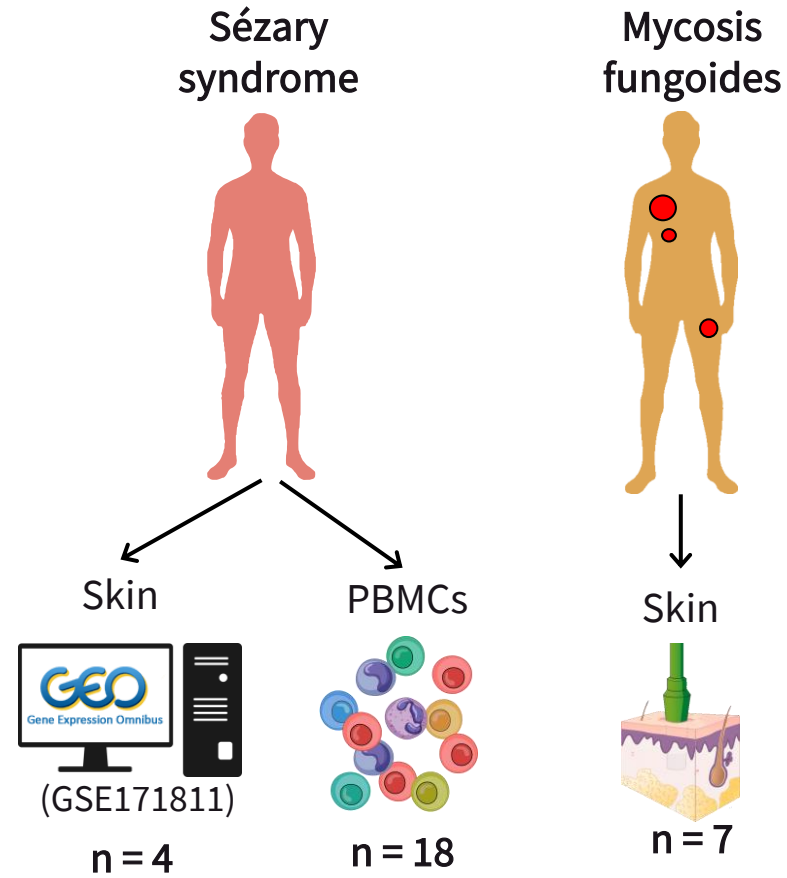


[LeBlanc RE. Mycosis Fungoides. *www.pathologyoutlines.com*. 2022]

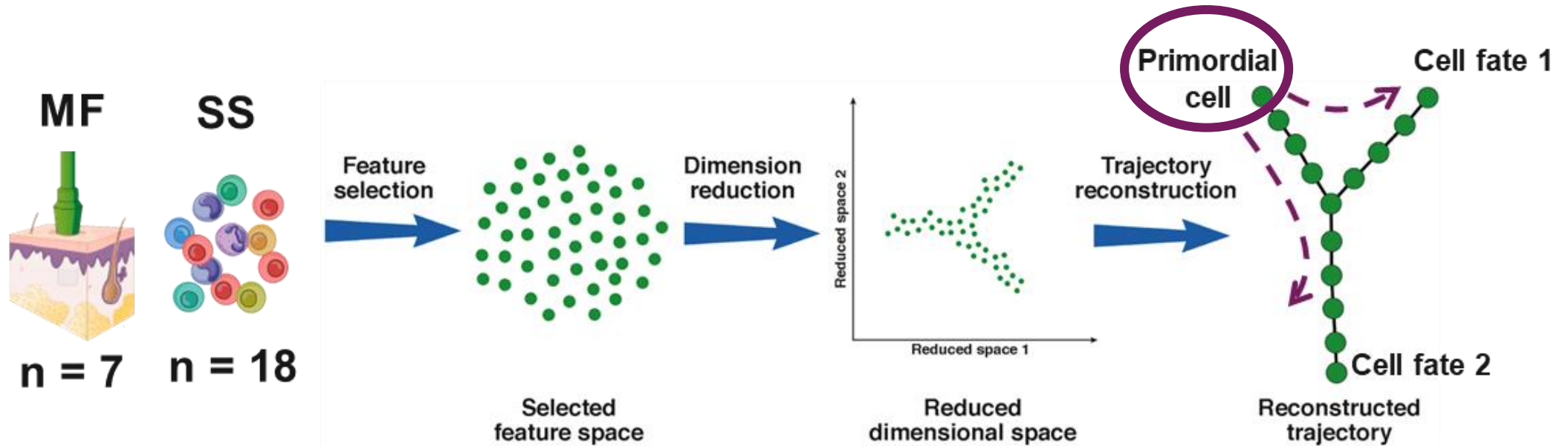
[Kamijo H, et al. *J Dermatol*. 2019; Lazarchick J *ASH Image Bank*. 2010]

A new approach to an old question

Single cell transcriptomics

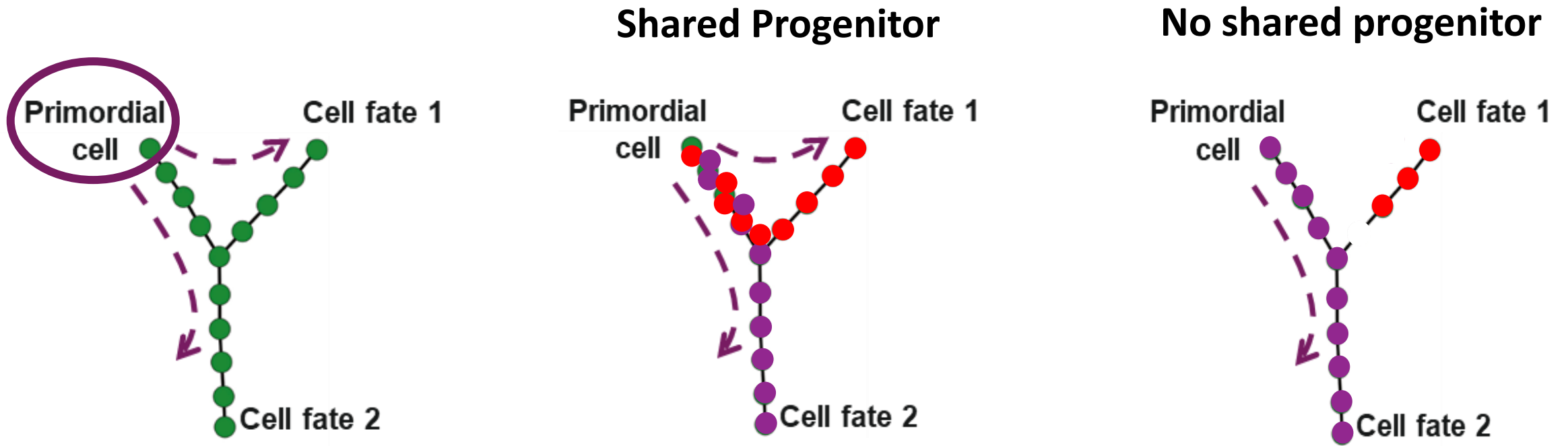


Monocle cell lineage reconstruction



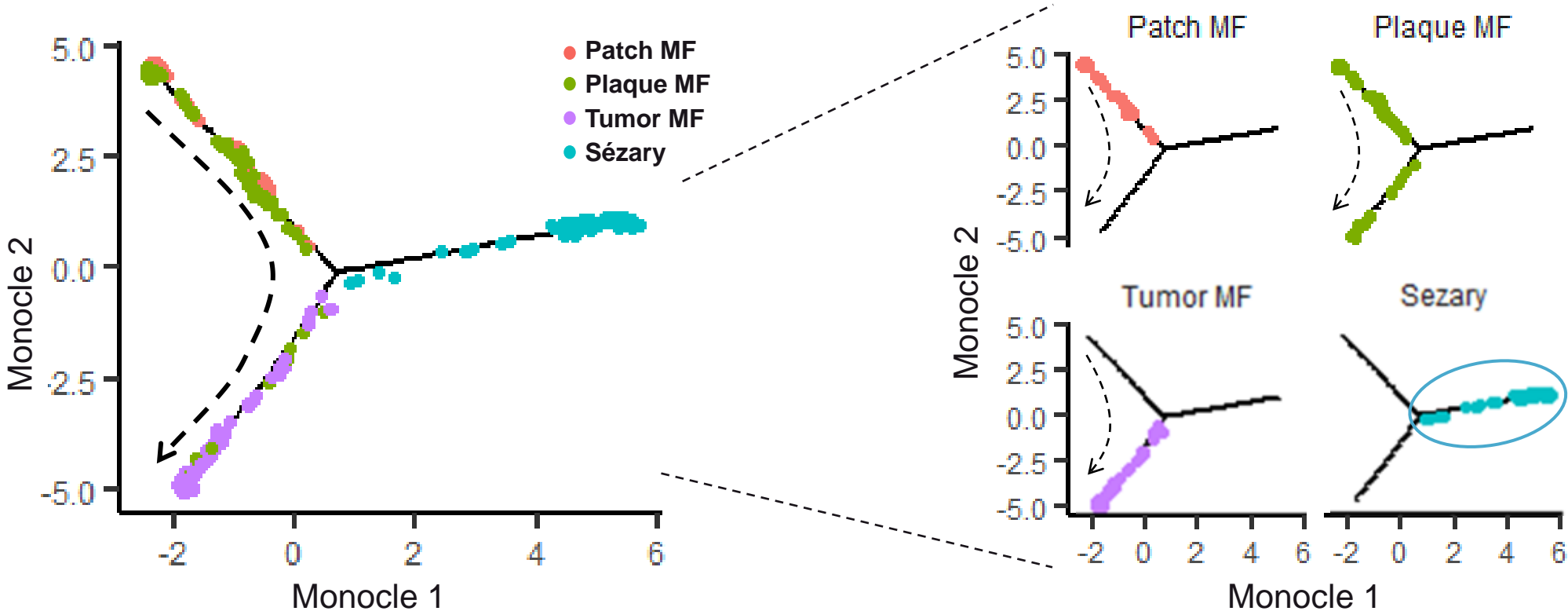
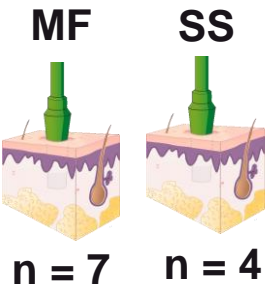
Using Monocle 2, we can use the heterogeneity captured by scRNAseq to predict a cell differentiation pathway

Do Sézary cells share a progenitor with MF?



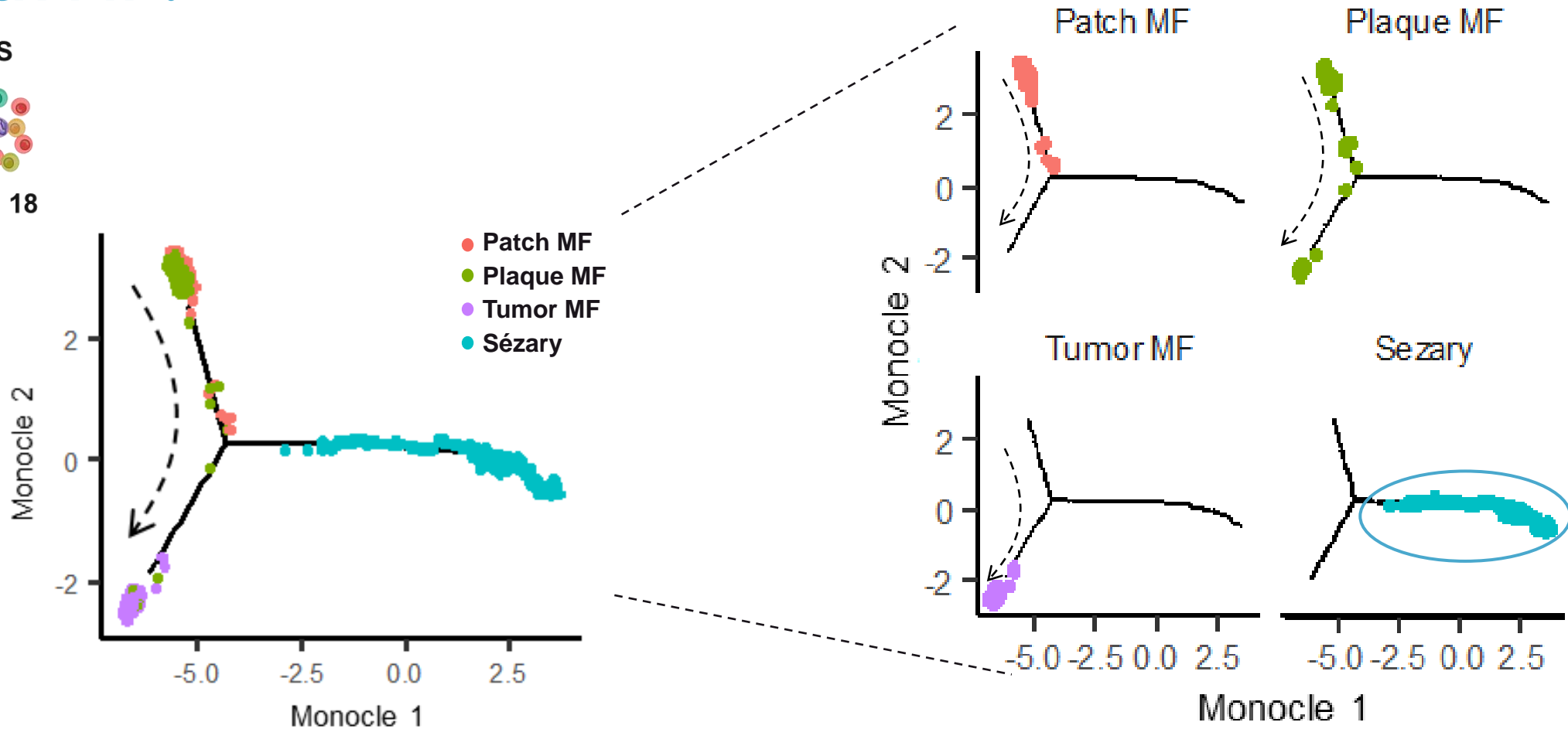
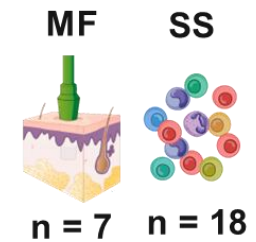
A branch with overlapping cells from MF or SS would indicate a shared precursor.

Do skin SS cells share a common progenitor with MF?



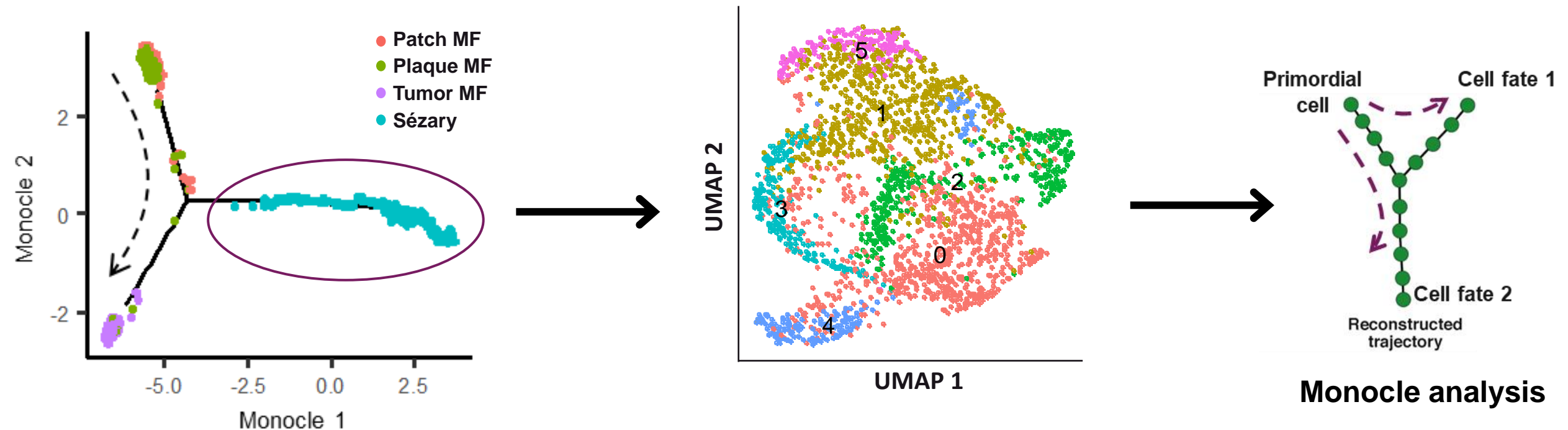
Skin malignant Sézary cells do not share a common progenitor cell with mycosis fungoides

Do peripheral blood Sézary cells share a common progenitor with MF?



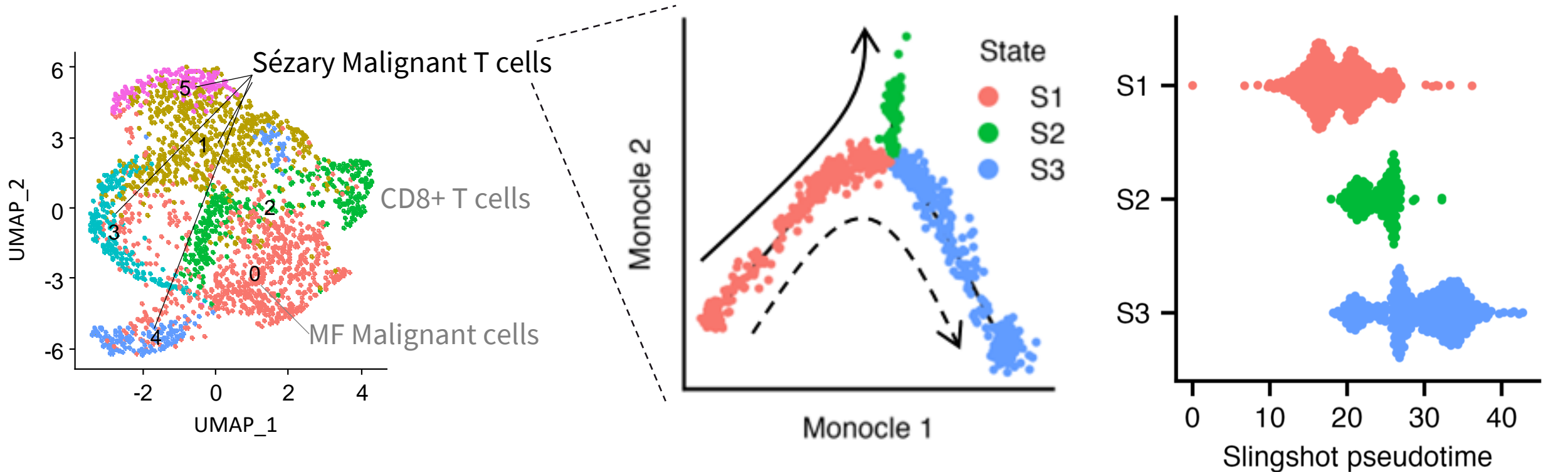
Sézary cells in blood do not share a common progenitor cell with mycosis fungoides

Deciphering heterogeneity: How are some malignant cells surviving treatment?



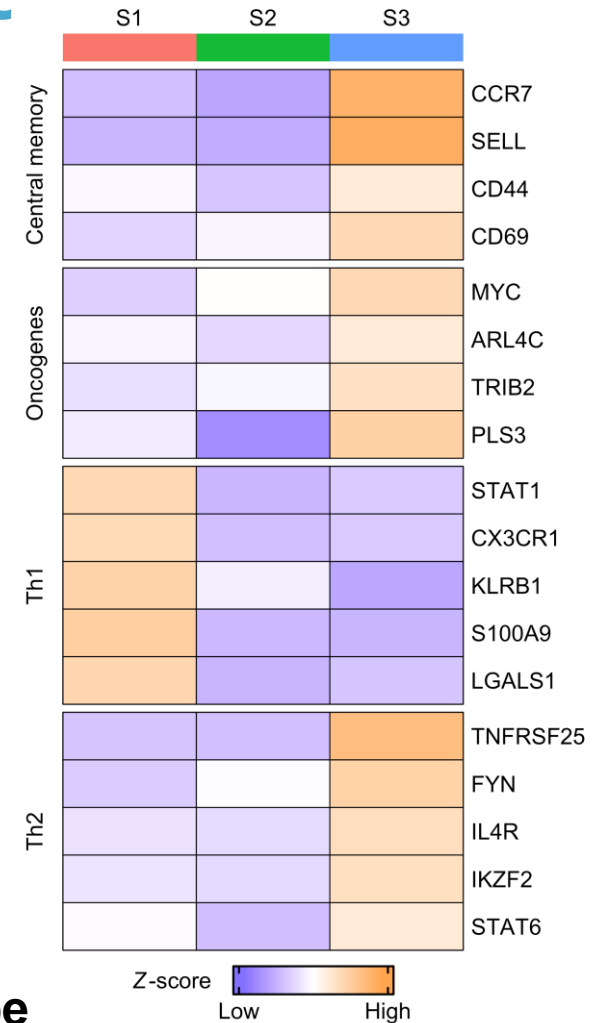
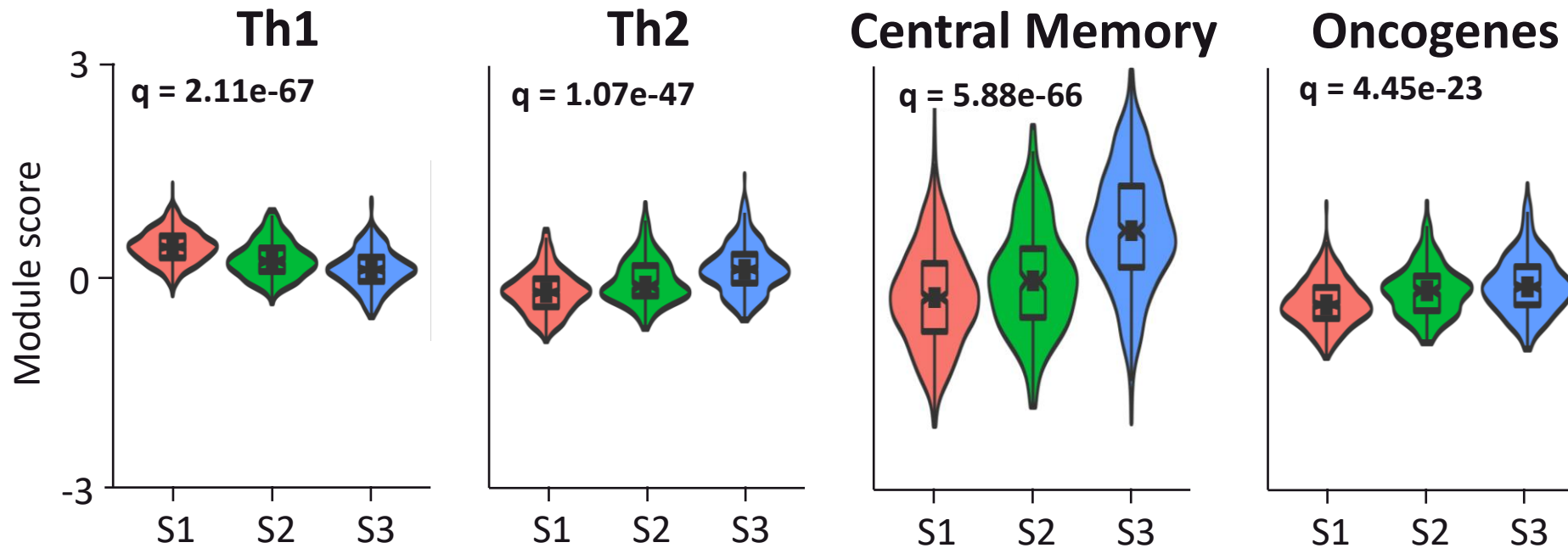
Could specific cell subsets contribute to treatment resistance?

Are there distinct Sézary cell subsets?



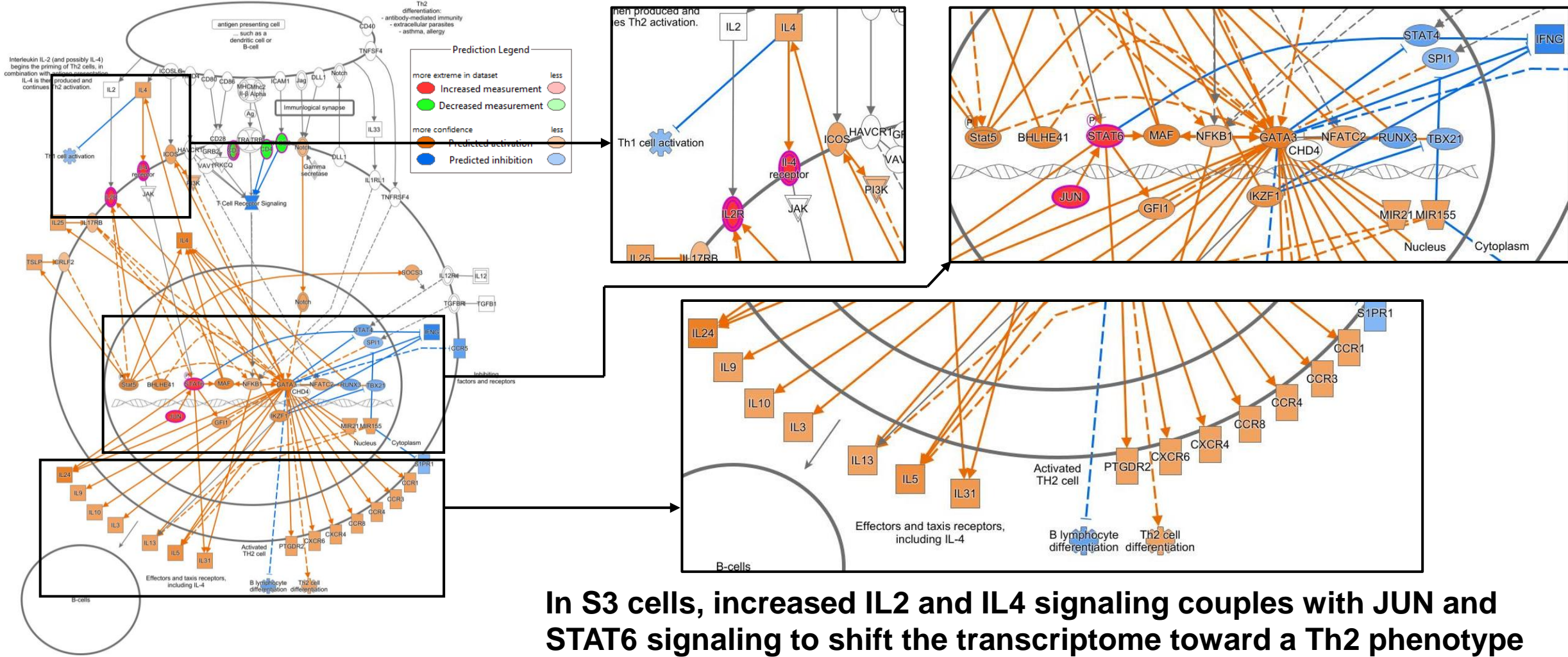
Monocle identifies three Sézary cell subsets, with the S1 phenostate as the primordial state and the S3 phenostate as the terminal state of differentiation

What are the transcriptional signatures of these states?



S1 is Th1 polarized, while S3 exhibits a Th2 polarized, central memory phenotype with increased oncogene expression

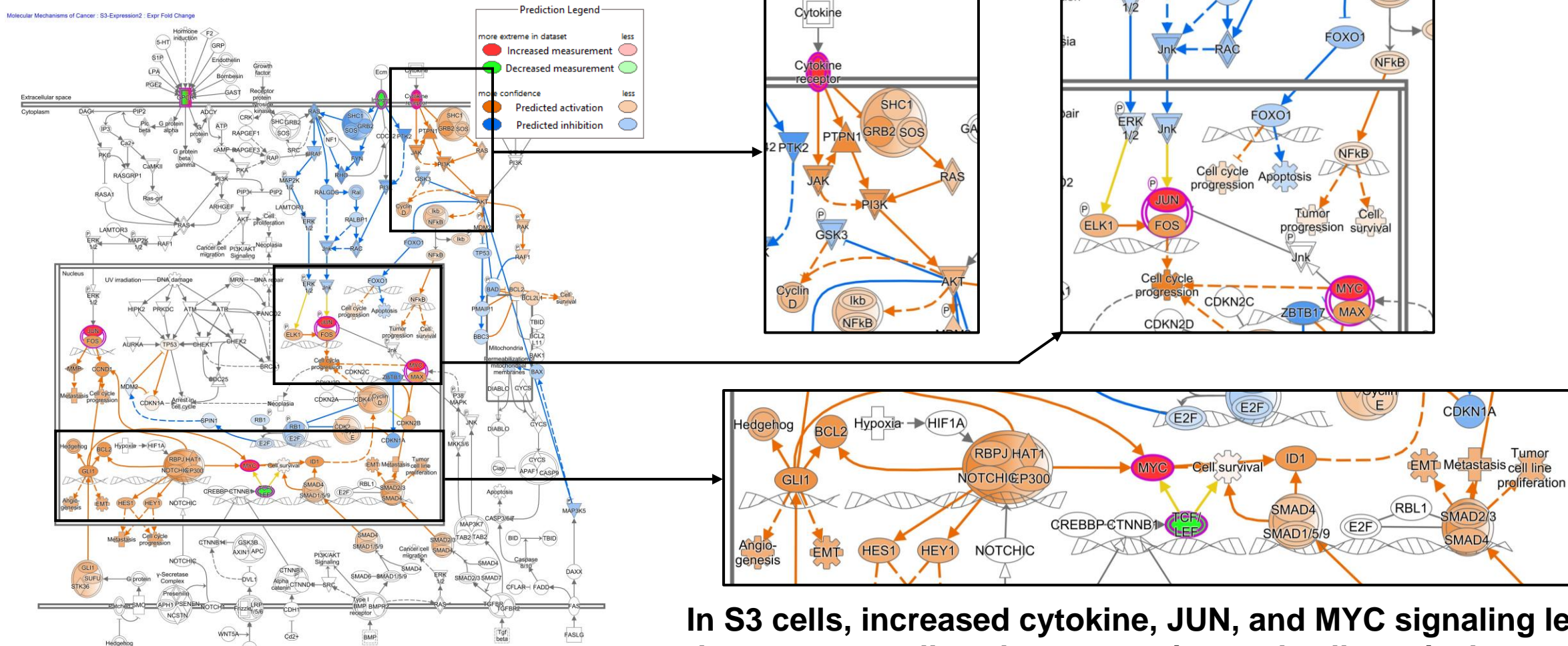
What molecular pathways are involved? Th2 activation in S3 subset



In S3 cells, increased IL2 and IL4 signaling couples with JUN and STAT6 signaling to shift the transcriptome toward a Th2 phenotype

What molecular pathways are involved? Oncogenes in S3 Subset

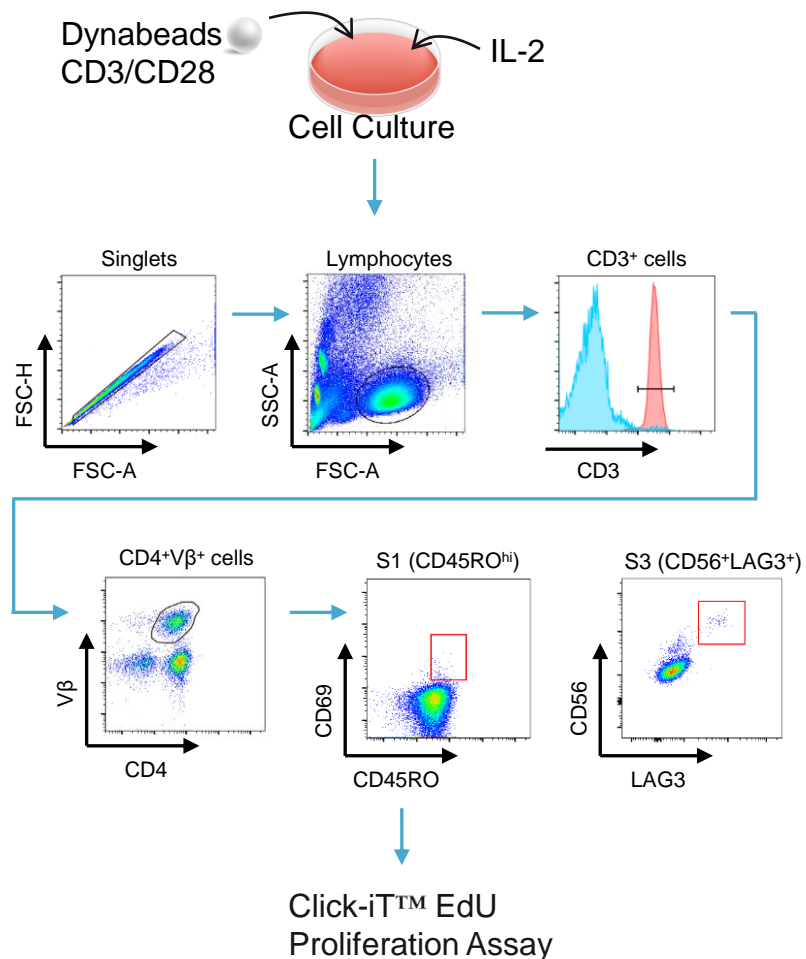
Molecular Mechanisms of Cancer: S3-Expression2_Expr Fold Change



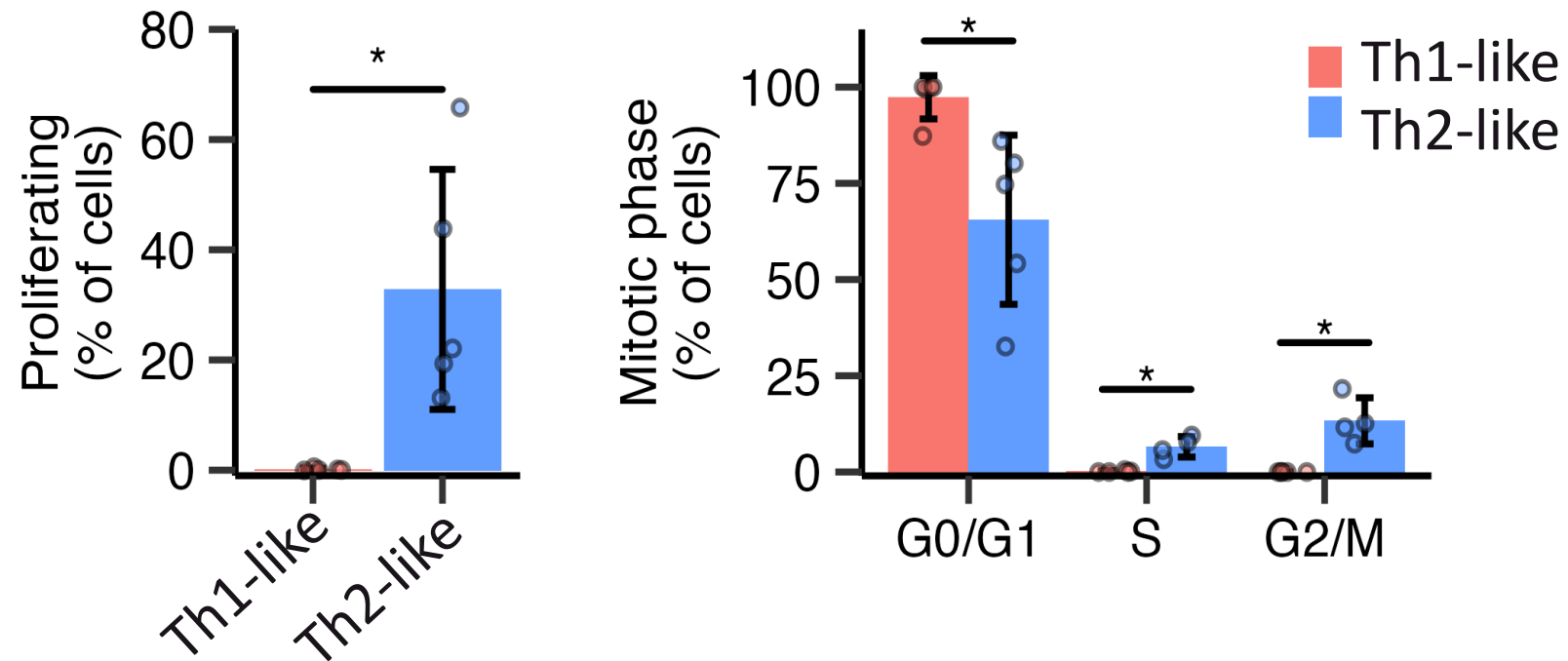
In S3 cells, increased cytokine, JUN, and MYC signaling lead to downstream cell cycle progression and cell survival

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Are these Sézary cell subsets real?

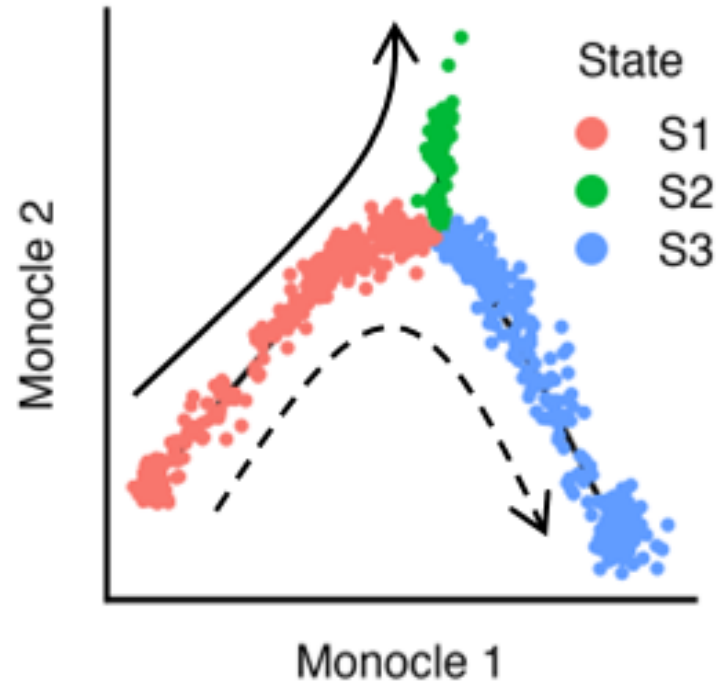
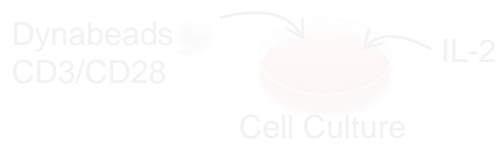


Cell Proliferation by Subset



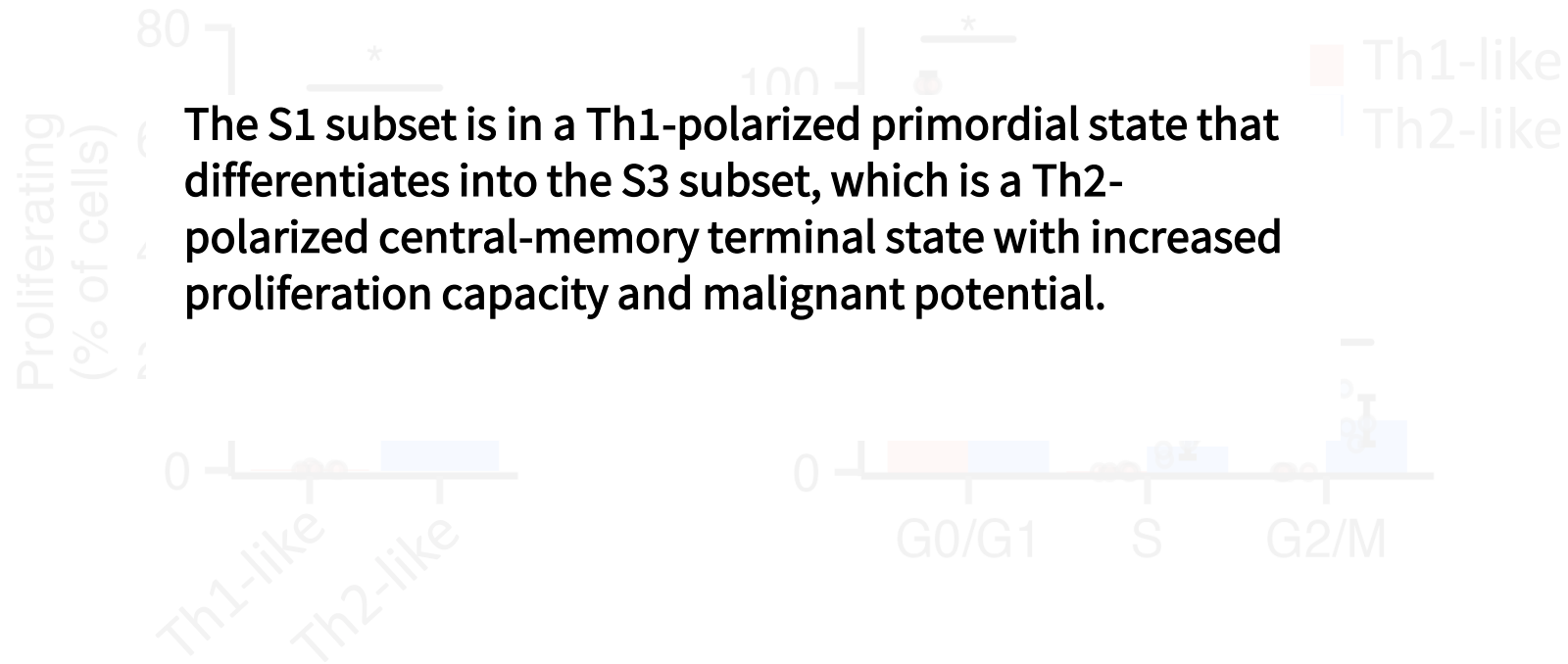
Th2-like cells have greater proliferation capacity than Th1-like cells, which are largely quiescent

Are these Sézary cell subsets real?



Click-iT™ EdU
Proliferation Assay

Cell Proliferation by Subset



Th2-like cells have greater proliferation capacity than Th1-like cells, which are largely quiescent

How do these cells respond to IL-4 and dupilumab?



Short Report | [Full Access](#)

Rapid and sustained control of itch and reduction in Th2 bias by dupilumab in a patient with Sézary syndrome

O. Steck, N.L. Bertschi, F. Luther, J. van den Berg, D.J. Winkel, A. Holbro, C. Schlapbach

First published: 17 October 2020 | <https://doi.org/10.1111/jdv.17001> | Citations: 22



CORRESPONDENCE | [Open Access](#) |

Dupilumab aggravates Sézary syndrome: The importance of accurate pathological diagnosis

[Home](#) > [American Journal of Clinical Dermatology](#) > Article

Development of Cutaneous T-Cell Lymphoma Following Biologic Treatment: A Systematic Review

Systematic Review | Published: 10 January 2023

Research letter

Diagnosis of mycosis fungoides or Sézary syndrome after dupilumab use: A systematic review

[Abdulahdi Jfri MD, MSc^{a b c d e}](#), [Jeffrey S. Smith MD, PhD^{a c f g h i}](#), [Cecilia Larocca MD^{a b c}](#)



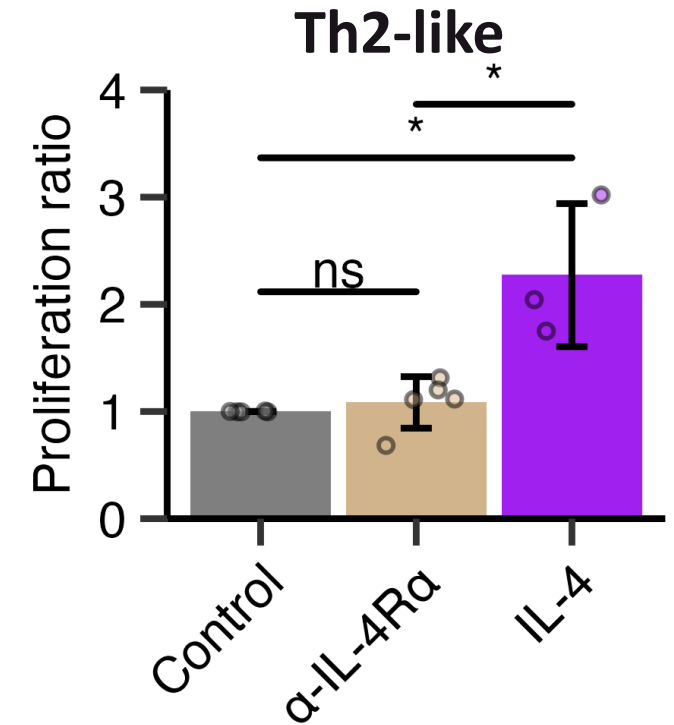
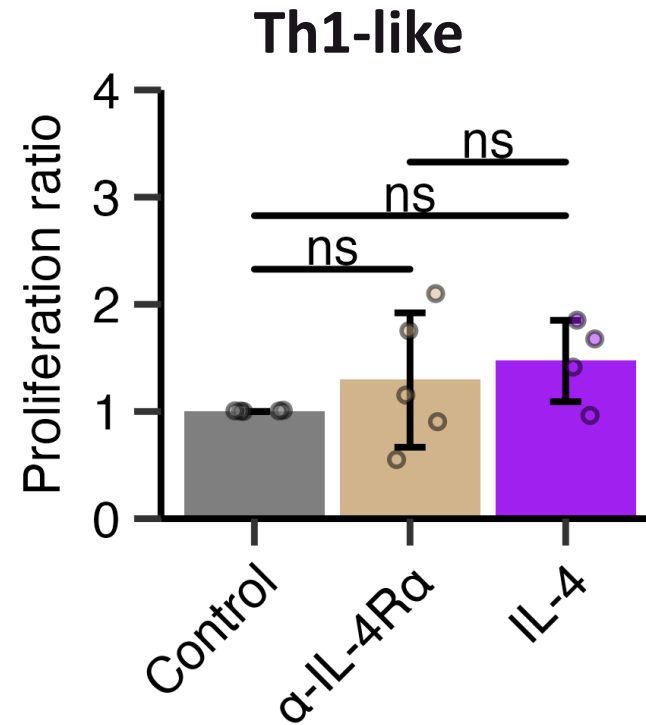
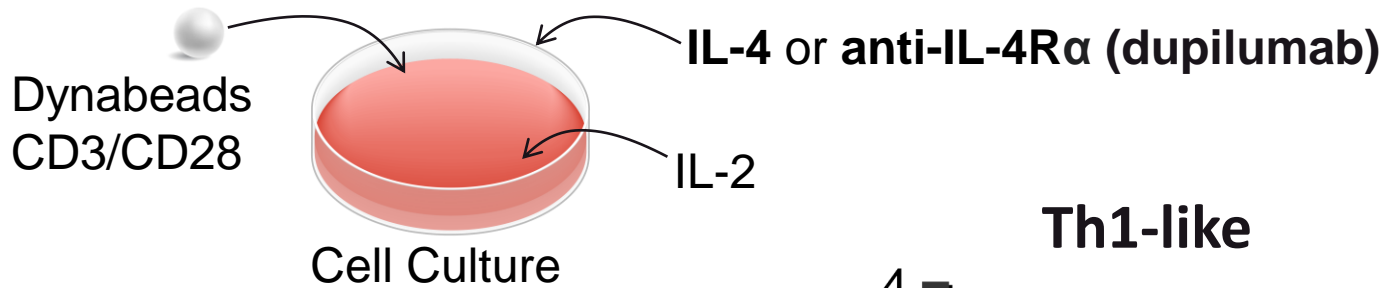
RESEARCH LETTER | VOLUME 83, ISSUE 1, P197-199, JULY 2020

Progression of cutaneous T-cell lymphoma after dupilumab: Case review of 7 patients

Maria L. Espinosa, BS • Morgan T. Nguyen, BA • Amaia Saenz Aguirre, MD • ... [Laura B. Pincus, MD](#) • [Joan Guitart, MD](#) • [Xiaolong A. Zhou, MD, MSc](#) • [Show all authors](#)

Case reports of Sezary syndrome treatment using dupilumab show brief remission, rapid disease progression, and even new disease onset

How do these cells respond to IL-4 and dupilumab?

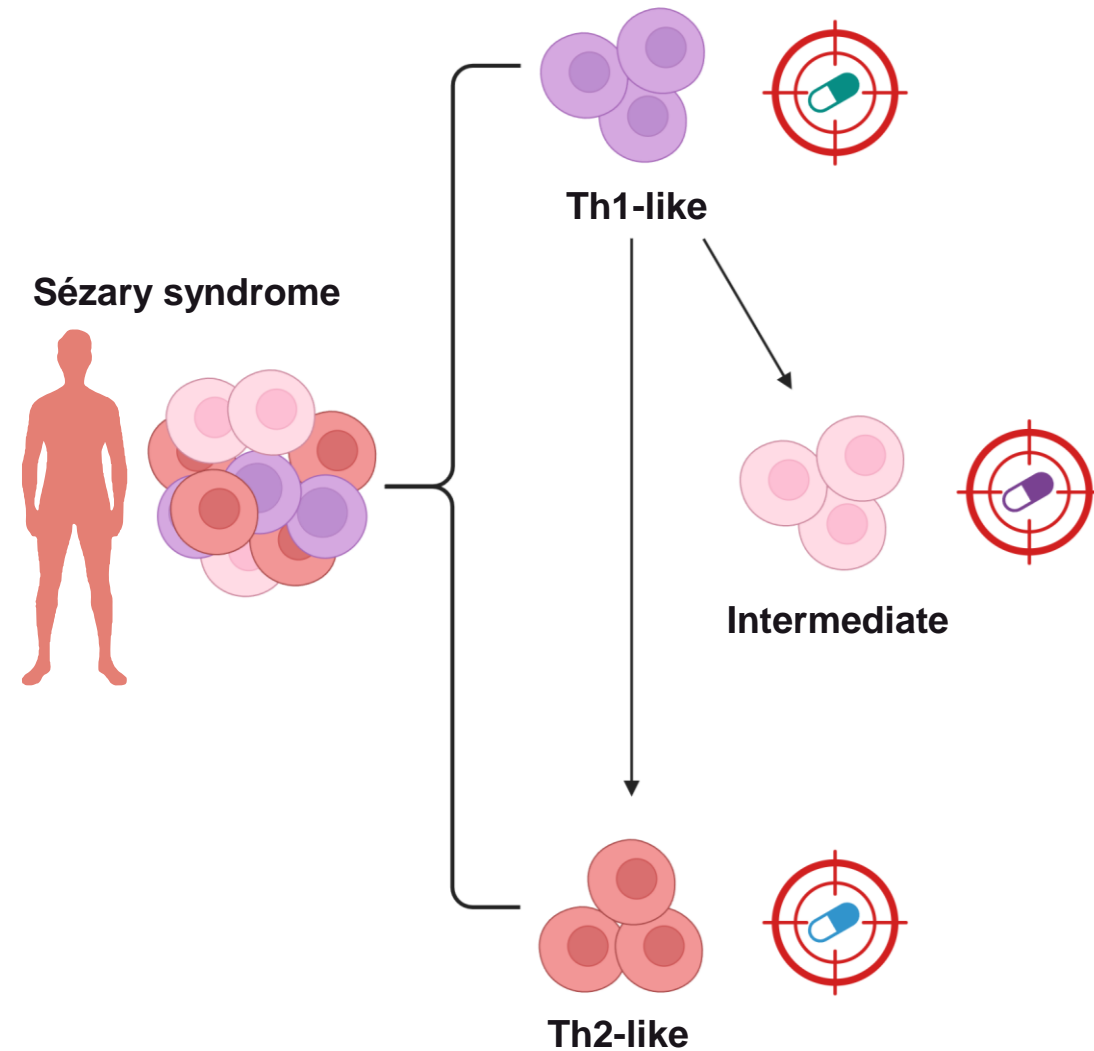


Th2-like cells proliferate in response to IL-4 while Th1-like cells do not

Dupilumab is ineffective on both cell subsets

Summary

- Through single cell lineage reconstruction, we provide further evidence that SS and MF are distinct entities
- Additionally, we find that heterogeneous malignant populations in SS are composed of subpopulations with different T helper polarizations
- Multi-targeted therapy may be necessary for successful control of Sézary syndrome



Thank you!



Dr. Jiang



Dr. Kruglov



A Virmani



Dr. Geskin



Dr. Falo



Dr. Akilov



Our Patients



HILLMAN FELLOWS
For Innovative Cancer Research Program

Martin and Dorothy
Spatz Foundation